

DISSERTATION

FOUNDATIONS OF EXECUTIVE FUNCTION IN DOWN SYNDROME

Submitted by

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In partial fulfillment of the requirements

For the Degree of Doctor of Philosophy

Colorado State University

Fort Collins, Colorado

Spring 2020

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## ABSTRACT

### FOUNDATIONS OF EXECUTIVE FUNCTION IN DOWN SYNDROME

Though early features of infant cognition are predictive of executive function (EF) in typically developing (TD) children, there is little information regarding the developmental origins of EF in Down syndrome (DS). The current study compared the performance of infants with DS and TD controls on four foundational EF dimensions: attention shifting, sustained attention, early planning, and processing speed, and examined the relationship between EF foundations at Time 1 and subsequent EF performance at Time 2 (6 months later). Participants were 58 infants with DS,  $M$  chronological age = 11.32 months,  $SD$  = 3.50;  $M$  developmental age = 7.93 months,  $SD$  = 2.79, and 48 TD infants,  $M$  chronological age = 7.76,  $SD$  = 3.22;  $M$  developmental age = 7.75 months,  $SD$  = 3.52. Results showed that infants with DS shifted their attention more slowly, looked for longer durations at objects, and demonstrated a longer latency to contact objects when compared to TD infants at Time 1. The association between early planning and chronological age differed by group at Time 1 as well. Attention shifting at Time 1 significantly predicted EF performance at Time 2 in the DS group. This study provides evidence that an early atypical presentation of EF precursors is detectable during infancy in DS and is predictive of subsequent EF performance. These findings will facilitate the identification of areas of early cognitive risk in DS and inform future interventions.

## ACKNOWLEDGEMENTS

I would like to express sincere gratitude to my advisor, Dr. Deborah Fidler, for the patient guidance, and encouragement that she has provided to me throughout the last five years. I would also like to thank my thesis committee member, Dr. Lisa Daunhauer, for her feedback and reassurance as I completed my dissertation work. Special thanks should be given to Dr. Susan Hepburn, her professional and clinical guidance was invaluable throughout my time as a student. I also would like to thank my outside department committee member, Dr. Andrew Knight, for his time and valuable insight on my project. My grateful thanks are also extended to Dr. Melissa George for her statistical support and recommendations for this project. I would also like to thank Dr. Amy Needham and Dr. Maninderjit Kaur for their help with data collection at Vanderbilt University.

I would also like to express my immeasurable appreciation to my parents, Chuck and Madge Schworer. You both have inspired me to pursue academic excellence and follow my passions in life. To my brother, Stephen Schworer, and his family (Katie, Madeline, and Walter), you bring so much joy to my life and I am thankful for you all. I am also extremely grateful for my fiancé, Sean Lindsay, and two best friends, Erin Maxwell and Lisa Mann, for keeping me laughing and providing endless support. Finally, I would also like to thank my current lab members. Their support was essential for the completion of my project.

This project was funded by the National Institute on Disability, Independent Living, and Rehabilitation Research (NIDILRR grant #90IF0096-01-00).

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## CHAPTER 1 INTRODUCTION

### **Summary**

Down syndrome (DS) is the most common chromosomal cause of intellectual disability and affects approximately 1 in every 691 live births in the United States per year (Parker et al., 2010). John Langdon Down first described DS in 1866, but it was not until 1959 that Jerome Lejeune discovered that DS was caused by the presence of a third 21<sup>st</sup> chromosome (Patterson & Costa, 2005). Individuals with DS are predisposed to a specific phenotypic profile that includes relative competencies in visual processing, receptive language, and nonverbal social functioning, and relative challenges in motor skills, expressive language, and auditory processing (Daunhauer & Fidler, 2011). In addition to general cognitive delays present throughout the lifespan in DS, there is growing evidence of specific impairment in the ‘executive functions’ (EFs) required for goal-directed behavior. At present, little is known about the developmental origins of EF challenges in DS. This dissertation project aims to advance our understanding of foundational EF skills in DS, to expand our understanding of early disruptions in cognitive development in this population, and to inform future targeted early intervention.

### **Executive Function**

‘Executive function’ is a term that refers to the cognitive skills required to attend to and complete goal-directed behavior. Although the component processes of EF continue to be debated, most EF models include (but are not limited to) the domains of working memory, inhibition, cognitive flexibility, and planning (Miyake, Friedman, Emerson, Witzki, & Howerter, 2000; Müller & Kerns, 2015). Working memory is one component of EF and refers to the capacity to hold and manipulate information. A second component, inhibition, involves

restraining or delaying impulses. Third, cognitive flexibility is the ability to switch between rules or sets of rules, and finally, planning is the organization of a sequence of steps to complete a task. Individuals depend on each of these four component processes to complete goal-directed behavior, with certain tasks relying more heavily on one area than another. These components are distinct and contribute differently to the completion of goal-oriented tasks, but also are related, as evidenced by the correlations among EF components (Miyake et al., 2000).

As an umbrella term, EF refers to the set of different cognitive processes necessary for completing goal-directed behaviors, and there is mounting evidence that throughout development, EF components become increasingly more dissociable (Brydges, Fox, Reid, & Anderson, 2014; Wiebe et al., 2011). Throughout the first 10 years of life, components of EF are closely intertwined, and confirmatory factor analyses supports a unitary model as the best fit for EF models in young children (Brydges et al., 2014; Shing, Lindenberger, Diamond, Li, & Davidson, 2010). At approximately age 10 in TD children, EF skills begin to become separable and confirmatory factor analyses provide evidence for a two or three factor EF model of dissociable constructs (Miyake et al., 2000; Shing et al., 2010). Thus, when studying young children, the differentiation of EF components is limited and the existing evidence supports the use of a unitary model to guide theoretical hypotheses related to EF foundational skill.

Once developed, EF skills tend to remain stable over time in children with TD (Carlson, Mandell, & Williams, 2004; Casey et al., 2011; Polderman et al., 2007). However, evidence of malleability has been reported in intervention and training studies (Diamond & Lee, 2011; Riggs, Greenberg, Kusché, & Pentz, 2006). This malleability is noteworthy, as it presents opportunities to improve upon EF in childhood, which in turn could impact school performance and academic achievement. There is still research needed to determine the long-term impact of EF training, but

there is potential that specific EF skills could be identified as therapeutic targets. Further, understanding foundational EF skills in infants may also lead to more timely implementation of supports for young children with challenges in this area.

### **Early Research on Goal-Directed Behavior in DS**

**Temperament.** Although research efforts specifically investigating EF in DS were not common before the early 2000s, research focusing on self-regulatory skills and goal-directed behavior has been central to the study of development in children with DS for several decades. Studies in the 1980s and 90s examined goal-directed behavior within the context of a variety of frameworks, including temperament and motivation (Gunn & Berry, 1985; Rothbart & Hanson, 1983; Ruskin, Mundy, Kasari, & Sigman, 1994). One early study of infant self-regulation from a temperament perspective used the Infant Behavior Questionnaire to examine infants 6-12 months old with DS and reported lower ratings of vocal reactivity and higher ratings of engagement with objects and fear when compared to TD infants (Rothbart & Hanson, 1983). These results gave early insight into patterns of reactivity and persistence in infants with DS, however, similar studies on infant temperament failed to replicate these findings. Contrary to the Rothbart and Hanson (1983) findings, young children with DS aged 4-36 months were reported to be less persistent than TD children (Bridges & Cicchetti, 1982; Gunn & Berry, 1985). Evidence for a less persistent profile has also been demonstrated in middle childhood and adolescence in DS as well (Gunn & Cuskelly, 1991). While patterns of behavior are clearer later in childhood, early conflicting findings in self-regulatory behavioral descriptions of infants with DS may result from the use of different temperament measurement tools and additional investigation is needed to continue to characterize early self-regulatory and goal-directed behavior in infants with DS.



**Motivation.** Another approach to understanding goal-directed behavior in DS has involved studies of engagement and child motivation. In a study measuring behaviors during a free-play task, children with DS exhibited shorter sequences of goal-directed action than mental age-matched TD children (Ruskin et al., 1994). Similarly, the rejection of toys was higher for children with DS in this study (Ruskin et al., 1994) and reports of refusal to engage with difficult tasks are common in the DS literature (Pitcairn & Wishart, 1994; Wishart, 1996; Wishart, 2001). In addition to the rejection of activities, children with DS use other techniques to avoid the completion of goal-oriented tasks. For example, social engagement often accompanies task refusal in children with DS and has been viewed by some researchers as an escape strategy (Kasari & Freeman, 2001; Pitcairn & Wishart, 1994). This line of research on engagement and motivation offers insights regarding goal-directed behavior in DS, however, work in this area does not examine the underlying factors that influence these challenges. It is important to further investigate the early starting states of goal-directed behavior in DS while continuing to consider engagement and motivation when interpreting studies directly examining EF.

### **Executive Function in DS**

Although there is value in studying goal-directed behavior from temperament and motivation perspectives, additional insight can be gained by examining EF, the cognitive factors that contribute to goal-directed behavior. A growing number of studies have identified global EF difficulties in DS when compared to mental age-matched individuals (Daunhauer et al., 2014; Daunhauer, Gerlach-McDonald, Will, & Fidler, 2017; Lanfranchi, Jerman, Dal Pont, Alberti, & Vianello, 2010; Lee et al., 2011; Rowe, Lavender, & Turk, 2006). Descriptions of global EF deficits in DS are complemented by research examining each domain of EF. While EF skills have not been found to be dissociable until age 10 in TD, there is potential for earlier

dissociability of EF in neurodevelopmental disorders (Ozonoff & Jensen, 1999). Different neurogenetic disorders present varying profiles of dysfunction related to EF constructs (Ozonoff & Jensen, 1999) and there is evidence of a syndrome-specific pattern of dissociable EF skills in DS (Daunhauer et al., 2014; Daunhauer et al., 2017; Edgin, 2003; Pennington, Moon, Edgin, Stedron, & Nadel, 2003; Rowe et al., 2006). By investigating each EF component individually, progress has been made towards a more thorough characterization of EF strengths and challenges in DS.

**Working memory.** There is substantial evidence that working memory, a subdomain of EF, is an area of pronounced challenge for individuals with DS (Carney, Brown, Henry, 2013; Daunhauer et al. 2017; Daunhauer et al., 2014; Lee et al., 2011). However, there is also complexity within this presentation. When comparing performances on verbal versus visuospatial working memory, studies show an advantage for visuospatial working memory in school-aged children, adolescents, and young adults with DS (Borella, Carretti, Lanfranchi, 2013; Lanfranchi, Baddeley, Gathercole, & Vianello, 2012; Lanfranchi, Cornoldi, & Vianello, 2004; Rowe et al., 2006).

Although it is generally accepted that spatial working memory performance is stronger than verbal working memory in DS, there remain instances where this profile is called into question. For example, multiple studies report similar levels of impairment on both verbal and spatial measures of working memory in adolescents with DS compared to TD children matched on IQ (Carney, Brown, Henry, 2013; Vicari, Carlesimo, & Caltagirone, 1995). Significant deficits in both spatial and verbal working memory have also been reported in adults with DS when compared to individuals with other developmental disabilities (Rowe et al., 2006). There are several reasons why studies on adolescents and adults with DS may have failed to replicate

the findings of an advantage for visuospatial working memory. Variations in study design elements, including measures, comparison groups, and participant age, likely contribute to the lack of replicated findings. It is important to continue to improve upon methods to address the potentially confounding factors and work towards a better understanding of the differences in processing of spatial versus verbal working memory tasks in DS.

In addition to working memory deficits observed in laboratory settings, working memory challenges in daily contexts are observed in EF studies that use parent or teacher-report measures of child behavior (Daunhauer et al., 2014; Gioia et al., 2000; Gioia et al. 2003; Lee et al., 2011; Loveall, Conners, Tungate, Hahn, & Osso, 2017). Specifically, parents of children with DS ages 2-5 years and ages 6-18 years report the greatest difficulties in the subdomain of working memory relative to other subdomains of EF in DS on the Behavior Rating Inventory of Executive Function (BRIEF; Loveall et al., 2017). Caregivers report that working memory deficits persist throughout the lifespan in DS, with working memory remaining an area of challenge in adulthood according to caregiver report (Loveall et al., 2017; Tomaszewski, Fidler, Talapatra, & Riley, 2018); Wilde & Oliver, 2017). Overall, there is strong empirical evidence of a working memory deficit for individuals with DS that begins early in the lifespan, however, there is a paucity of research related to how working memory deficits emerge in infancy and toddlerhood. By characterizing the early disruptions of EF in DS, insight may be gained related to the mechanisms that lead to challenges with working memory in daily contexts.

**Inhibition.** Inhibition has been studied throughout the lifespan in DS and there is a lack of converging findings that suggest some degree of within-group variability on this dimension. One of the earliest investigations of inhibition in DS examined preschooler behavior during a delayed reward inhibition task (Kopp, Krakow, & Johnson, 1983). In comparison to TD controls,

young children with DS demonstrated a decreased latency to make contact with the reward presented, suggesting that there may be challenges with the development of inhibitory control in DS (Kopp et al., 1983). Another study found that adolescents with DS also experience difficulty with inhibition when compared to mental age-matched TD adolescents, both on measures of general inhibitory control, and specifically on tasks that involved suppressing irrelevant information (Borella et al., 2013). These reports offer converging evidence for inhibitory control deficits in children and adolescents with DS.

Although there are some clear findings of inhibition deficits, reports of child performance on inhibition tasks can often be confounded by working memory demands, which must be taken into account when interpreting results because of pervasive working memory deficits in DS. For example, working memory and inhibition were measured in a task similar to “Simon Says,” in which participants were to respond to simple motor requests from the “nice pony” and inhibit simple motor requests from the “gruff gator” (Daunhauer et al., 2017). In this study, school-aged children with DS correctly inhibited fewer responses when compared to mental age matched TD children (Daunhauer et al. 2017). These findings provide evidence for challenges with inhibitory control in childhood, but results could also have been a function of working memory deficits. Similarly, inhibition has been tested in adults with DS using a finger-tapping task where participants were asked to tap their fingers twice if the examiner tapped once, and tap once if the examiner tapped twice (Rowe et al., 2006). The adults with DS repeated the examiner’s finger tapping, rather than following the rules of the task, more often than adults with intellectual disabilities (Rowe et al., 2006). Again, these findings may have resulted from inhibitory control deficits, but they may also be rooted in working memory challenges as well (Rowe et al. 2006).

Although there are numerous reports of inhibition challenges in DS, there are studies that suggest that inhibition skills are, in fact, on par with overall developmental status in DS. In one study, children and adolescents with DS were found to perform similarly to a developmentally matched TD group on verbal and visuospatial modified Stroop inhibition tasks (Carney et al., 2013). This study provided evidence for a relative strength in the basic response inhibition skills required for both verbal and visuospatial inhibition tasks (Carney et al., 2013). Inhibition strengths have also been reported in studies examining caregiver and teacher report questionnaires. In one study, although parents reported deficits with inhibition relative to developmental norms, teachers did not identify inhibition as an area of challenge in children with DS (Daunhauer et al., 2014). Similarly, inhibition was identified as an area of relative strength in adults with DS by caregivers who completed the adult version of the BRIEF (Tomaszewski et al., 2018). Taken together, there are no clear converging findings in this area and therefore, inhibition should continue to be an area of investigation in individuals with DS to determine how best to support the development of this subdomain of EF in this population.

**Cognitive flexibility.** Although there are conflicting findings related to the presentation of inhibitory control skills in DS, there is consistent evidence of challenges in the area of cognitive flexibility throughout the lifespan. Cognitive flexibility is commonly assessed using a dimensional change card-sorting task (DCCS; Zelazo, & Jacques, 1996; Zelazo, 2006). In this task, participants are required to sort based on one feature of a picture (i.e., shape), then switch to another feature of the picture (i.e., color), and finally follow multiple rules simultaneously. Children, adolescents, and young adults with DS show challenges in shifting on the DCCS task when compared to developmentally equated TD children, children with developmental disabilities and children with Williams syndrome (Campbell et al., 2013; Edgin, 2003; Rowe et

al., 2006; Zelazo, Burack, Benedetto, & Frye, 1996). Questionnaire ratings also provide supporting evidence for deficits in shifting skills in children and adults with DS (Loveall et al., 2017). While the majority of findings demonstrate that cognitive flexibility is an area of challenge, one study of preschoolers with DS reported cognitive flexibility performances that were similar to young TD children equated on receptive language abilities (Roberts & Richmond, 2015). This study did not use the DCCS laboratory measure, but rather a simpler version of a cognitive shifting task, the A-not-B task (Roberts & Richmond, 2015). It may be the case that simple switching skills develop with competence in young children with DS, yet, deficits with more sophisticated rule-following and shifting are commonly observed in this population.

**Planning.** Planning is the organization of a sequence of behaviors to reach a goal and requires the integration of component skills of EF (i.e., working memory, inhibition, and cognitive flexibility). Although there are some instances where challenges are not reported (Costanzo et al., 2013; Pennington et al., 2003), planning is often described to be an area of significant challenge for children with DS. In one study involving early strategizing, young children with DS ages 2-4 years produced poorer quality strategies during an object retrieval task than TD children and children with developmental disabilities equated on mental age (Fidler, Hepburn, Mankin, & Rogers, 2005). Similar planning challenges are also observable in school-aged children with DS. Kasari and Freeman (2001) found that children with DS exhibited less task persistence and took longer to complete puzzles than TD and intellectual disability comparison groups. Additionally, school-aged children with DS are less likely to engage with new objects (Daunhauer et al., 2017; Fidler, Will, Daunhauer, Gerlach-McDonald, & Visootsak, 2014) and produce less novel functional acts on objects during object-related generativity

planning tasks (Fidler et al., 2014). This lack of generativity is suggestive of deficits in the planning skills required to interact with new objects in functional ways. Caregiver reports also identify planning as an area of challenge, which provides further evidence that this domain is a weakness relative to overall developmental status in DS (Daunhauer et al., 2014; Lee et al., 2011). Thus, there is convincing evidence of planning deficits for individuals with DS, warranting further investigation into the foundational skills that may be connected to these challenges.

### **Early Measures of Executive Function**

Although the majority of the studies reviewed thus far have focused on school-age children with DS, it is also possible to measure EF during earlier stages of development. The A-not-B task is the most common method used to measure cognitive flexibility, inhibition, and working memory in TD infants and toddlers ages 10-36 months (Blankenship et al., 2019; Bernier, Carlson, Deschenes, & Matte-Gagne, 2012; Carlson, 2005; Diamond, 1985; Johansson et al., 2016; Kochanska et al., 2000; Miller & Marcovitch, 2015). One measurement tool is typically used to assess multiple EF components in young children because, as previously discussed, EF presents as a unitary model in infancy and toddlerhood (Brydges et al., 2014; Shing et al., 2010). Studying the earliest presentations of EF is critical for understanding how goal-directed skills emerge in early childhood.

The A-not-B task is a search task that requires a child to shift the location of their search across trials. In the task, there are two locations where an object can be hidden. The examiner hides the object in location “A” and asks the child to retrieve it. Accepted responses from the child include reaching toward the location or other forms of manual searches where the object was hidden. This procedure is repeated multiple times, with the object hidden in location “A,”

before moving the object to location “B” and asking the child to reach for or retrieve it.

Performance on the A-not-B task improves linearly over the first three years of life in TD children (Diamond, 1985). Infants with TD as young as 8 months begin to pass the A-not-B task without error if the delay before a response is shorter than 2 seconds (Diamond, 1985). Gradually children with TD can tolerate longer delays after the objects are hidden (Diamond, 1985), which reflects cognitive growth in the area of memory and inhibition required to complete shifting tasks throughout infancy and toddlerhood.

Reported shifting performance varies based on specific task demands on two types of A-not-B assessment procedures (Cuevas & Bell, 2010; Kovács & Mehler, 2009). One way that A-not-B has been administered and interpreted involves gaze-dependent task demands. In one study that used a gaze-dependent task, infants with TD were trained to anticipate stimuli on one side of a screen and in test trials, the location of the stimuli switched (Kovács & Mehler, 2009). Seven and 8-month old TD infants were consistently able to shift to the new location of the stimuli, demonstrating competence in a visual version of shifting measurement (Kovács & Mehler, 2009). By reducing the task demands to include only visual demands, the inhibition of anticipatory eye movements were measured, and foundational cognitive flexibility skills were assessed without the motoric demands of the classic A-not-B task. In a second approach, two versions of the A-not-B task were administered to examine early EF, one that required visual responses and another that required manual responses (Cuevas & Bell, 2010). Cuevas and Bell (2010) compared visual and manual responses and determined that the visual performance of 5-8-month-olds with TD was similar to the reaching performance of 9-10-month-olds with TD. The differences in performance based on the design features of the measurement tool highlight the variability in possible results depending on the exact procedures used to administer the A-



not-B task. The measurement techniques of cognitive flexibility are critical for the study design, especially in populations with motor delays, such as DS.

**Early Executive Function in DS.** As previously described, there is strong evidence for challenges with early EF skills in DS (Daunhauer et al., 2014; Fidler et al., 2005; Kopp et al., 1983; Lanfranchi et al., 2012) coupled with modest evidence that suggests early EF competence in this population (Roberts & Richmond, 2015). No significant differences in A-not-B performance were reported on post-switch trials for young children, ages 3, 4 and 5 years with DS when compared to TD children equated on receptive language level (Roberts & Richmond, 2015). Mean inspection for this study, however, shows that young children with DS did have lower proportions of correct responses than TD children (Roberts & Richmond, 2015). Thus, while there is evidence of early EF competence on the A-not-B task in children with DS, more work is needed to more thoroughly characterize the earliest presentations of EF in this population.

### **Significance of Studying Foundations of EF**

EF challenges have important clinical implications, as EF performance is strongly associated with a range of critical outcomes in both TD and clinical populations (Best, Miller, & Naglieri, 2011; Cahn-Weiner, Boyle, & Malloy, 2002; Riggs, Jahromi, Razza, Dillworth-Bart, & Mueller, 2006). In children with DS, EF is predictive of adaptive outcomes and academic achievement, and in adulthood, EF predicts employment status (Daunhauer et al., 2017; Tomaszewski et al., 2018; Will, Fidler, Daunhauer, & Gerlach-McDonald, 2017). Because of the profound impact that EF has on school performance and achievement, there is a need to better understand the foundations of EF in their earliest presentations so that initial disruptions in cognitive development can be identified. The past two decades of developmental science in

neurogenetic syndromes have provided evidence of the importance of understanding early starting states and developmental trajectories for critical outcomes, such as EF (Fidler, Lunkenheimer, & Hahn, 2011; Karmiloff-Smith et al., 2012). This work is hypothesized to facilitate phenotype-informed early intervention approaches, which offer the potential for downstream impact on developmental outcomes for individuals with intellectual and developmental disabilities (Edgin, Clark, Massand, & Karmiloff-Smith, 2015). Recent support for this theoretical framework comes from the Ts65Dn mouse model of DS, where early targeted treatment has been shown to impact later learning and memory performance (Das et al., 2013). As early treatment science moves forward, further investigation is needed to identify foundational skills that facilitate more adaptive developmental outcomes. To support early EF competencies, infant cognitive skills that precede dysregulated EF in DS need to be characterized. Describing early cognitive performance in infants with DS will be a critical first step to ultimately identifying the foundational skills that predict later EF outcomes.

### **Infant Foundations of EF**

Advances in early developmental science in the TD literature may serve as an important guide for research on the mechanisms underlying the emergence of EF challenges in DS. In recent work, researchers have identified hypothesized precursors of EF that can be measured during infancy, including control of attention, processing speed, cognitive flexibility, and self-regulation (Hendry, Jones, & Charman, 2016). There is growing evidence that performance in each of these areas in infancy is predictive of later EF performance in TD school-aged children and adolescents (Garon, Smith, & Bryson, 2014; Kochanska, Murray, & Harlan, 2000; Rose, Feldman, & Jankowski, 2012; Rothbart, Sheese, Rueda, & Posner, 2011). This preliminary work on the developmental origins of EF in TD infants can serve as a guide for examining infant

precursors to dysregulated EF in DS. By examining the cognitive foundations of EF identified in the TD literature (Devine, Ribner, & Hughes, 2019; Hendry et al., 2016), it will be possible to capitalize on recent advances in early developmental science to address unanswered questions regarding the emergence of EF vulnerabilities in young children with DS. The following sections provide a review of the existing knowledge in this area and describes the developmental time windows of mastering these skills, which will inform the examination of early challenges in infants with DS related to the emergence of EF.

**Attention shifting.** The ability to attend to stimuli, sustain attention, and resist distractors develops during the first year of life in TD infants (Rothbart et al., 2011; Ruff & Rothbart, 1996). Early on, infants with TD show preferences for novel stimuli (Fantz, 1964; Weizmann, Cohen, & Pratt, 1971), and as the attentional system becomes more refined, infants at 4 months can shift attention from one stimulus to another (Johnson, Posner, & Rothbart, 1991). Prior to 4 months, however, infants have more difficulty with disengaging from stimuli, and this lack of gaze shifting is referred to as “sticky fixation” (Atkinson, Hood, Wattam-Bell, & Braddick, 1992; Johnson et al., 1991; Kulke, Atkinson, Braddick, 2017). The presence of multiple stimuli also slows infant attention shifting speed (Kulke et al., 2017). The latency to shift attention when competing targets are present decreases over the first few months of infancy, until about 5 to 7 months, in TD infants when shifting latencies do not differ based on the presence or absence of competing stimuli (Atkinson et al., 1992; Kulke et al., 2017).

The development of attention shifting and factors that affect variability in performance are important for understanding self-regulation in infants and EF in particular. Faster disengagement of attention at 6 months has been shown to be associated with lower infant distress, an early indicator of self-regulatory behavior (McConnell & Bryson, 2005). This

association provides support for the connection between early attention shifting and emerging EF skills. However, by the age of 2 years, the converse is true, and slower disengagement is related to early self-regulatory behavior (Nakagawa & Sukigara, 2013). These results are likely due to more advanced resistance to distractors that develops in the toddler years, which allows for greater overall control of attention.

**Sustained attention.** The ability to sustain attention and resist distractors progresses rapidly during infancy and is also related to later EF skills (Blankenship et al., 2019; Devine, Ribner, & Hughes, 2019; Holmboe, Fearon, Csibra, Tucker, & Johnson, 2008; Johansson et al., 2015; Kannass, Oakes, & Shaddy, 2006; Kochanska et al., 2000; Ruff & Lawson, 1990). Sustained attention is generally measured by examining an infant's directed attention toward an object during free play activities (Gaertner, Spinrad, & Eisenberg, 2008; Johansson et al., 2015; Kannass et al., 2006). Over the first five years of development, focused attention increases linearly (Kannass et al., 2006; Ruff & Lawson, 1990) and one study found that focused attention at one year predicted later parent report of self-regulatory behavior at two years in TD infants (Johansson et al., 2015). Attention at 4 months has also been connected to laboratory-based outcomes on early measures of EF at 14 months in TD infants. These relationships persist into early childhood and one study reported that infant sustained attention and shifting rate at 5-months were predictive of EF skills at 3, 4, and 6 years-old (Blankenship et al., 2019). These studies provide evidence for a strong connection between early attention and EF performance and support the hypothesis that EF skill development builds upon early attention regulatory processes present in infancy.

In addition to predicting overall EF performance, sustained attention in infancy (9 and 12 months) also predicts performance on the A-not-B task in follow-up assessments during

toddlerhood (Johansson et al., 2015; Kochanska et al., 2000). While longitudinal evidence was presented for this association in two separate studies, there were differences in the timing of EF related outcomes reported. In one study, infant sustained attention predicted EF at 22 months, but not 33 months (Kochanska et al., 2000), however, in the other longitudinal study, sustained attention predicted EF at 36 months, but not 24 months (Johansson et al., 2015). These conflicting findings suggest that early attention may have predictive value for later EF performance, however, additional research is needed to determine the best timing for measurement of these effects. Regardless of the timing of longitudinal outcomes, there is consistent evidence that sustained attention and attention shifting are central skills that contribute to the differences in child EF performance (Garon et al., 2008; Johansson et al., 2015; Kochanska et al., 2000) and these constructs will be examined as foundational infant cognitive skills in the current study.

**Processing speed.** Processing speed refers to the time that it takes to encode and complete a cognitive task (Canfield et al., 1997). In TD infants, both habituation studies and saccade reaction time studies are used to measure processing speed (Hendry et al., 2016). Saccade reaction time tasks measure the latency for eye movements to reach a target stimulus after presentation (Canfield et al., 1997) and habituation tasks use the duration an infant spends looking at an object to quantify the amount of time infants spend encoding the object (Colombo & Mitchell, 2009; Stoecker, Colombo, Frick & Ryther, 1998). Both types of measurement provide evidence of increasing processing speed between 2 and 6 months in TD (Canfield et al., 1997; Colombo & Mitchell, 2009). Processing speed is a critical cognitive ability in infancy and numerous studies connect early processing speed to later cognitive functioning and intelligence

(Bornstein et al., 2006; Bornstein & Benasich, 1986; Lewis & Brooks-Gunn, 1981; Rose et al., 1988).

Though habituation is not considered to be a measure of intelligence in infants, the cognitive processing foundations of habituation are strongly related and essential for cognitive growth and EF. Improvements in working memory are mediated by increases in processing speed (Fry & Hale, 1996), which demonstrates the association between this basic neuropsychological skill and EF components. Additionally, faster processing speed at 5 months, quantified by average looking time to a stimulus, is associated with stronger EF performances at 24, 36, and 48 months in TD children (Cuevas and Bell, 2014). There is also evidence that the association between infant processing speed and EF persists throughout development. Rose, Feldman, and Jankowski (2012) measured infant processing speed using both saccade reaction times and a habituation task at 7 and 12 months and found that early processing performance was related to cognitive flexibility at 11 years old. Thus, there is strong evidence that processing speed is connected to EF development and is an important cognitive skill to examine in the context of foundational EF skills in infancy.

### **Early Manifestations of Goal-directed Behavior**

The infant literature reviewed thus far highlights previously investigated early precursors of later EF (i.e., attention and processing speed). In addition to examining these EF precursors, it may be equally informative to identify and characterize the earliest forms of goal-directedness and planning in infancy. Because EF is not measurable until approximately age two or three in TD children, capturing early forms of planning during infancy poses a challenge. During the first year of life, infants are unable to complete the multistep tasks commonly used to assess this area of EF skill. Despite the inability to perform EF planning tasks, the development of cognitive

regulation occurs throughout infancy and can be measured in the form of more foundational goal-directed actions, including early volitional acts on objects (Bridgett et al., 2011; Elsner & Hommel, 2001; Kopp, 1982). Long before multi-step planning tasks can be performed, infants demonstrate organized, purposeful behavior in their desire to obtain objects for exploration. These early volitional acts on objects are manifested in the form of reaching.

Reaching behavior is a fitting candidate as an early form of planning because it involves elements of goal-directedness and intentional behavior. The production of a planful act requires that an infant select and hold a goal in mind (i.e., the desire to secure a toy) and produce an action to make progress toward that goal (i.e., reach for a toy). Previous studies provide evidence that infants have the capability to represent goals and interpret actions as goal-directed within the first year of life (Csibra, 2008; Daum, Prinz, Aschersleben, 2008; Woodward, 1998). This evidence of early goal representation is complemented by direct connections made in the mirror neuron literature between infants' observations of goal-directed action and subsequent motor responses (Robson & Kuhlmeier, 2016). In one study, when infants observed a goal-directed action, their motor system was activated (Southgate, Johnson, Karoui, & Csibra, 2010). This motor activation was not observed when viewing ambiguous actions, and thus demonstrates a clear link between goal representation and the motor system in infancy (Southgate et al., 2010). Reaching is an integral part of early planning and subsequent aspects of EF rely on these foundational skills for engagement in goal-directed behavior.

Early planful actions may also have further implications for the continued development of more advanced EF skills. Multiple studies show that early enrichment with reaching experiences in TD pre-reaching infants leads to greater object engagement later in development (Libertus, Joh, & Needham, 2016; Needham, Barrett, & Peterman, 2002). These studies suggest

that by facilitating infants' object-related action, a cascading effect is initiated on successive developmental outcomes, and may, in turn, be related to cognitive skill acquisition more broadly. Therefore, reaching is an important construct to examine within the context of infant foundational EF skill to evaluate if this form of early goal-directed behavior is predictive of later EF performance.

### **Foundations of EF in DS**

Evidence for the relationship between neuropsychological foundations and EF skills in TD children raises the question of whether disruptions in EF can be traced back to the early cognitive presentations during infancy in clinical populations. The current study aims to examine attention, processing speed, and early planning collectively to better understand the origins of EF disruptions in infants with DS. Currently, there is limited information on these dimensions in DS, especially in infants, and more research is needed to improve the identification of early risk in this population. Despite the limited quantity, there have been studies that begin to characterize the early profile of attention, processing speed, and early planning in infants and toddlers with DS and the following sections will cover what is already known about these EF foundations specifically in infants with this neurogenetic syndrome.

**Attention.** Although attention in DS has been examined for several decades, there is only a small number of studies examining early attention regulation in infants with DS. One recent study demonstrated a positive correlation between attention shifting and overall cognitive skill acquisition in infants with DS (Fidler, Schworer, Will, Patel, & Daunhauer, 2019). The description of this relationship is important because it identifies early attention shifting as a potentially critical construct for cognitive growth in infants with DS. In addition to attention shifting, sustained attention is also described in studies examining object interest in young



children with DS. Multiple studies have found that infants and toddlers with DS engage in less attention to objects, focus attention for shorter periods, and spend more time unoccupied during play compared to developmentally equated TD infants and toddlers (Brown et al., 2003; Krakow & Kopp, 1982; Krakow & Kopp, 1983; Legerstee & Weintraub, 1997). Taken together, these studies suggest that there are challenges with attention during this early developmental period in DS and more research is needed to determine whether there are potential broader effects on cognition. Continuing to characterize early disruption in the development of attention shifting and sustained attention in infants with DS will be one important part of understanding foundational cognitive skills in this population.

**Processing speed.** In addition to delays in early attention skills, delays in processing speed have also been observed in infants with DS. In one study, infants with DS were found to be significantly delayed in the development of habituation, a measure of processing speed, and did not demonstrate this skill until 8 months on average (Lewis & Brooks-Gunn, 1984). Further information is needed to characterize the trajectory of early processing speed in infants with DS. The addition of work aimed to investigate processing speed with habituation paradigms in DS will build upon our knowledge regarding the profile of strengths and challenges within early cognition in infants with DS.

**Early planning.** Finally, while there is a small quantity of information on early goal-directed planning in infants with DS, there are studies that begin to describe this skillset. One study found that infants with DS produced grasping actions less frequently than TD infants matched on chronological age (CA; de Campos et al., 2013). Although overall variations in motor ability were not controlled for, a quantitative difference between groups in action towards objects in infancy was reported (de Campos et al., 2013). Toddlers with DS also demonstrate

challenges with object retrieval planning, which provides further evidence for an early disruption of goal-directed action in DS (Fidler et al., 2005). Taken together, these findings provide an initial look at the early challenges with goal-directed regulatory behavior in DS. To address the need for more research in this area, the current study aims to characterize the developmental foundations of goal-directed action and early planning in DS. Because there is considerably less information available about the timetable of mastery for EF foundational skills in DS compared to TD infants, the current study also examined the relationship between each area of potential early cognitive risk and CA.

### **The Current Study**

In this study, the early foundations of EF were examined in infants with DS and TD controls, with the long-term goal of optimizing targeted early intervention for individuals with DS and identifying early disruptions in cognition that may be connected to comorbid conditions more broadly. Specifically, the study compared the performance of infants with DS and TD controls on four foundational EF dimensions: attention shifting, sustained attention, processing speed, and early planning at Time 1. Although these skills have been examined separately in TD infants, this study was the first to examine the set of cognitive skills in both TD and DS samples. This comparison of infants with DS to TD controls revealed areas of early cognitive risk within DS. Next, the relationship between CA and the set of infant foundational EF skills was examined at Time 1. By describing this relationship, it is possible to determine the strength of the connection between CA and overall developmental risk in DS. Finally, the longitudinal associations between EF precursors and early EF performance were assessed in infants with DS. Investigating the underpinnings of EF skills in DS will add to the growing scientific knowledge

base regarding cognitive precursors to later EF skills, and facilitate the identification of cognitive risk and key targets for early intervention in young children with DS.

## CHAPTER 2 METHODS

## Overview

The current project leveraged resources from a federally-funded intervention project (National Institute of Disability, Independent Living, and Rehabilitation Research; NIDILRR #90IF0096-01-00) focused on the early development of goal-directed behavior in young children with DS. The measures in the current study were administered to infants with DS at two time points as per the NIDILRR study's longitudinal design. A sample of TD infants of similar cognitive levels was also included in the present study. TD infants were not included in the larger longitudinal study, but did participate in a comparable assessment battery (similar length, number of measures).

## Participants

The participants were 58 infants with DS and 48 TD infants. At Time 1, participants in the DS group were 5-17 months old,  $M$  chronological age (CA) = 11.32 months,  $SD$  = 3.50, and the TD participants were 3-13 months old,  $M$  CA = 7.76,  $SD$  = 3.22. Participant groups were equated on cognitive level using the Bayley Scales for Infants and Toddler Development (BSID-III; Bayley, 2006). The DS group had a similar cognitive level,  $M$  developmental age (DA) = 7.93 months,  $SD$  = 2.79, to the TD group,  $M$  DA = 7.75 months,  $SD$  = 3.52. Infants at this developmental level were habituating to pictures, exploring objects, and the majority (91%) were persistently reaching. One-way ANOVA results indicated that participants with DS were well equated to the TD group,  $F(1,104) = .09$ ,  $p = .77$ ,  $\eta^2 = .0008$ , and the sample had a variance ratio of .63 (Kover & Atwood 2013; Mervis & Klein-Tasman 2004). A variance ratio of less than one is expected, even in this equated sample, due to the commonly observed pattern of greater variance among children with DS compared to TD children (Karmiloff-Smith et al. 2016). The

examination of the  $p$ -value, effect size, and variance ratio are all recommended for group matching in the field of intellectual and developmental disabilities research (Kover & Atwood 2013; Mervis & Klein-Tasman 2004). Both groups included an approximately equal number of male and female participants (see Table 1). Exclusion criteria included severe hearing loss, serious visual impairment, or concurrent treatment for acute otitis media. Documentation of trisomy 21 was provided by parent report in the group of infants with DS. See Table 1 for full participant demographics.

**Time 2: 6-month follow-up.** A portion of the infants with DS also participated in a 6-month follow-up ( $n = 40$ ), and early EF performance was evaluated. At Time 2, infants with DS were 11-24 months old,  $MCA = 17.26$  months,  $SD = 3.55$ . The mean cognitive age of the participants with DS at Time 2 was 11.48 months,  $SD = 2.99$ . Prior to the 6-month follow-up, 23 infants participated in a goal-directed reaching intervention, and 14 of those 23 infants were assigned to the treatment condition. Participation in the reaching intervention was controlled for in all longitudinal analyses (see Fidler et al., [under review] for intervention results). Infants who participated in the 6-month follow-up did not have significantly different cognitive performance at Time 1 when compared to infants who did not participate in the second time point,  $t(56) = 1.44, p = .16$ . In terms of the differing sample size between Time 1 and Time 2 visits, eight infants were not re-contacted, five were lost due to attrition, three were not seen due to travel restrictions, one infant refused to complete the EF outcome task measured at Time 2, and one was not seen due to illness.

Table 1  
*Characteristics of Infant Participants*

	Mean (SD) or %	
	DS ( <i>n</i> = 58)	TD ( <i>n</i> = 48)
Chronological Age Visit 1	11.32 (3.50)	7.76 (3.22)
BSID-III Cognitive DA Visit 1	7.93 (2.79)	7.75 (3.52)
Chronological Age Visit 2 ( <i>n</i> = 40)	17.26 (3.55)	-
BSID-III Cognitive DA Visit 2 ( <i>n</i> = 40)	11.48 (2.99)	-
Child gender (% male)	50%	48%
Race		
White	84.6%	85.3%
Asian	3.4%	4.2%
Black/African American	1.7%	6.3%
More than one race	6.9%	4.2%
Unreported (missing)	3.4%	-
Ethnicity		
Hispanic or Latino	17.2%	4.2%
Not Hispanic or Latino	70.7%	91.6%
Unknown or unreported	12.1%	4.2%

There were two recruitment sites for this study. One site recruited all infants with DS (Colorado State University) and two sites recruited TD infants (Colorado State University and Vanderbilt University). Participants with DS were recruited through regional Down syndrome associations, clinics, and support groups in Southeast and Midwest regions of the United States and western Canada. Some infants in the TD sample were recruited through on-campus resources at Colorado State University, through the Early Childhood Center (ECC) and other local advertisements (*n*= 20). Colleagues at Vanderbilt University collected the second set of TD infants (*n*= 28). At Vanderbilt University, TD participants were recruited through birth records received from the state of Tennessee and through word of mouth. The set of laboratory tasks administered across sites was comparable, with one exception. Infants recruited at Colorado State University were administered all five BSID-III (Bayley, 2006) domains, however, infants

recruited at Vanderbilt University completed only the Cognitive domain of the BSID-III. All other procedures relevant to this project were identical.

## **Procedure**

The project leader obtained informed consent from the caregiver before completing the study tasks. Participants were seated on their caregiver's lap during the administration of each laboratory task and supported around their torso by the hands of their caregiver as necessary. Following the administration of the proposed battery of foundational cognitive laboratory tasks, children participated in a developmental assessment. Time for breaks was allotted to avoid any discomfort that may be experienced by the participants while completing play-based tasks. Data collection procedures for Time 1 and Time 2 did not differ in for the group of infants with DS.

This project used phenotype-appropriate measures to assess precursors to EF in DS observable during the first two years of life. Assessments minimized motor and language demands, areas of distinct challenge for many individuals with DS. With these considerations, the phenotype-sensitive measures for this study were chosen to capture early precursors of later EF performance (Hendry, Jones, & Charman, 2016).

## **Measures**

**Developmental abilities.** The Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III; Bayley, 2006) is a standard assessment used to measure Cognitive, Receptive Language, Expressive Language, Fine Motor, and Gross Motor developmental domains in children ages 1-42 months. This measure has been standardized with a sample of 1,700 children in the United States and has high internal consistency (.86-.93) and test-retest reliability (.80-.87; (Bayley, 2006). Adequate concurrent validity has been shown between the Wechsler Preschool

and Primary Scale of Intelligence-Third Edition and the BSID-III cognitive and language scales (.71-.83). The Cognitive domain of the BSID-III was used to equate groups.

**Foundational EF skills.** Foundations of EF were assessed using four laboratory tasks. Coders were trained on each of the following laboratory assessments to achieve and maintain inter-rater reliability (Cohen's Kappa) for 30% of the sample for each task. All coders were naive to the study hypotheses and a kappa of .70 was set as the minimum criteria for reliability. Coders met with the project leader bi-weekly to address any discrepancies in reliability.

*Attention Shifting.* A red ball and schematic face were held approximately 7-8 inches from the child's eyes, with the red ball 4 inches to the left of the child's midline and the schematic face 4 inches to the right of the child's midline (Mullen, 1995). Both objects were within the child's visual field. The examiner shook the red ball to attract the child's attention. After the child localized on the red ball, the examiner shook the schematic face. The examiner then alternated between the red ball and the schematic face, shaking each object several times (at least 2 trials on each side; Mullen, 1995). Both attention orienting (Colombo, 2001) and disengagement of attention (Elsabbagh et al., 2013) were captured in this task. Ocular reaction time was coded similarly to previous studies and has been shown to be a valid measure of attention shifting (Colombo, 2001; Hood & Atkinson, 1993; Hunnius & Geuze, 2004; Kulke, Atkinson, & Braddick, 2017; Rothbart, Ziaie, & O'Boyle, 1992; Stifter & Braungart, 1995). The latency to shift attention was coded and averaged across trials. Average kappa statistics were high, indicating strong inter-rater agreement (Cohen's Kappa = .93; Landis & Koch 1977; Cohen 1960). The distribution of this variable was found to be positively skewed and a log transformation was used to achieve a normal distribution of scores.



*Sustained Attention.* Focused attention was measured using an infant exploration task. A red teether with multiple textures was placed at the mid-line in front of the infant (Needham, et al., 2002). The examiner allowed for free exploration of the teether for approximately one minute. Total visual attention to the teether was coded. The amount of time that the infant had the teether in front of them (opportunity) was also calculated to control for trials that varied in time and provided a precise description of the percentage of the total time the infant was visually oriented to the teether during the task (Rose et al., 2012). Average kappa statistics were high indicating strong inter-rater agreement (Cohen's Kappa = .88; Landis & Koch 1977; Cohen 1960).

*Processing Speed.* Processing speed was measured using a classic habituation task. One child-sized spoon was placed in front of the infant in a series of three 30-second trials. Between each trial, the experimenter placed the object underneath the table so that the child would not know whether the object was the same one as in previous trials. Visual exploration across the three trials was coded. Difference scores between trial 1 and trial 3 were calculated (Barten & Ronch, 1971). Reverse scoring was also used to allow for scores to be interpreted in the same direction as the other variables (i.e., a larger number indicating more impairment). Any difference score above 100 indicated that the infant did not habituate to the spoon, and difference scores below 100 indicated the infant did habituate. Average kappa statistics were high, reflecting strong inter-rater agreement (Cohen's Kappa = .85; Landis & Koch 1977; Cohen 1960).

*Early Planning.* Early planning was measured with a reaching task (Barrett et al., 2008). Two balls, each with different properties (varying soft textures) were placed in front of the child at midline, one at a time, throughout the task. The experimenter presented each ball for free

exploration and retrieved the ball after 30 seconds elapsed. Latency to contact each ball was coded. Average kappa statistics were high, indicating strong inter-rater agreement (Cohen's Kappa = .98; Landis & Koch 1977; Cohen 1960).

The distribution for this variable was found to be positively skewed, and was subsequently recoded to achieve a normal distribution of scores. Six categories were generated, ranging from 1 (infants who made contact most quickly) to 6 (infants who made contact the slowest). A latency of 0-.60 was coded 1, .61-.75 was coded 2, .76-1.5 was coded 3, 1.51-3.0 was coded 4, 3.1-10.0 was coded 5, and 10.1-30.0 was coded 6. The scale also included the value 7 for infants who did not make contact with either ball.

**Early EF performance.** This study used the A-not-B task to estimate early EF abilities at Time 2. The A-not-B task is one of the earliest tests of EF for young children (Diamond, 1985). To set up the task, the examiner placed two washcloths, side by side, in front of the infant (location-A and location-B). The washcloths were just out of reach from the infant. The examiner then shook a colorful rattle to gain the infant's attention and placed it under the location-A washcloth. The examiner then pushed both washcloths toward the infant and encouraged the infant to "find the toy." After the infant pulled either one or both cloths, the trial was repeated twice more, hiding the colorful rattle in location-A. On the fourth trial, the location of the toy was switched to the second washcloth, location-B.

The infant responses on the fourth trial were coded and there were four categories of responses: "only location-B," "both locations, correct," "both locations, incorrect," and "only location-A." First, "only location-B" was coded if the infant manually pulled only the location-B washcloth. There were also instances where the infant pulled both washcloths. These observations were separated into a "both locations, correct" category when the infant pulled

location-B at least 1 second before pulling location-A, or a “both locations, incorrect” category when the infant pulled the location-A washcloth first. If the infant pulled both washcloths at the same time, “both locations, incorrect” was coded. The final category of infant response was “only location-A,” which was coded if the infant manually pulled only the location-A washcloth. Correct responses included “only location-B” and “both locations, correct”. Incorrect responses included “both locations, incorrect,” “only location-A,” and the absence of a manual search. Coders were naïve to the hypotheses for the study and demonstrated reliable inter-rater agreement (Cohen’s Kappa = .88; Landis & Koch 1977; Cohen 1960) for 30% of the sample.

### **Plan of Analysis**

The current study had three main goals: (1) to characterize group differences in performance on foundational EF tasks (attention shifting, sustained attention, processing speed, and early planning) in infants with DS and TD controls equated by group on overall cognitive level, (2) to quantify the relationship between CA and EF foundations in infants with DS and equated TD controls, and (3) to examine the association between cognitive foundational skill and early EF abilities in DS. Group differences were analyzed using *t*-tests and Mann-Whitney U tests, when appropriate. Bivariate Pearson correlations and multivariate multiple regression were used to test the association between CA and EF foundations. Binary-logistic regression was used to test the relationship between EF foundations and early EF outcomes at Time 2.

**Specific aim 1: Group differences. Goal.** Characterize the performance on EF precursor tasks (attention shifting, sustained attention, processing speed, and early planning) in young children with DS and TD controls equated by group on cognitive level at Time 1. **Hypothesis.** Although there is no existing empirical work examining these specific characteristics in young children with DS, based on reported EF deficits in older children with DS (Daunhauer et al.,

2014; Lee et al., 2011), it was hypothesized that all of these early foundational skills would also be impaired relative to the equated TD group. Specifically, it was posited that young children with DS would display slower attentional shifting, shorter durations of sustained attention, slower processing speed, and challenges with early planning. **Statistical Plan.** Hypotheses for specific aim 1 were tested using *t*-tests and Mann-Whitney U tests to compare performance between groups on each of the four foundational EF tasks.

**Specific aim 2: Foundational EF skills and chronological age. Goal.** Test the association between CA and EF foundational skills in infants with DS and equated TD controls at Time 1. **Hypothesis.** It was hypothesized that there would be a significant relationship between CA and foundational EF performance. We expected that the relationship between CA and the EF precursors would be moderated by group, such that the TD group would have a stronger relationship between CA and EF foundations and the group of infants with DS would have a modest relationship between the two variables. The stronger hypothesized relationship in the TD group is supported by existing literature that describes a strong association between EF and CA (Garon et al., 2014). A modest relationship was hypothesized in the group of children with DS because of the developmental heterogeneity observed in DS (Karmiloff-Smith et al. 2016).

**Statistical Plan.** The relationship between CA and EF foundations was tested using bivariate Pearson correlations and multivariate multiple regression with group as a moderator. The use of multivariate multiple regression allowed for the examination of the relationship between a set of independent variables (CA, diagnostic status, and CA x diagnostic status interaction) and a set of dependent variables (attention shifting, sustained attention, and early planning) and provided type I error protection.

### **Specific aim 3: Relationship between EF foundations and early EF skills in DS.**

**Goal.** Examine the longitudinal relationship between proposed cognitive foundational skills and early EF in DS. **Hypothesis.** It was hypothesized that infant cognitive foundations would be significant predictors of early EF at Time 2 in young children with DS. Early cognitive and attention skills in TD infants have been connected to EF outcomes in early childhood and adolescence (Cuevas & Bell, 2014; Johansson et al., 2015; Rose et al., 2012) and therefore, we expected to observe a similar pattern of association in young children with DS. **Statistical Plan.** The relationship between EF cognitive foundations and early EF skill in DS was tested using binary logistic regression. This statistical test was used because the early EF outcome variable was binomial (success or failure on the A-not-B task) and allowed for covariates (i.e., cognitive level and intervention condition) to be entered into the regression model.

**Power analyses.** GPower was used to calculate effect sizes based on the proposed sample (Faul, Erdfelder, Lang, & Buchner, 2007). Power analyses were calculated separately for each specific aim, as two types of analyses were used. With 58 participants in the DS group and 48 participants in the TD group and the power level set to .80, results indicated sensitivity to detect large effects (using *t*-test analyses and regression).

## CHAPTER 3 RESULTS

### Overall Description of Task Performance

Because of the lack of basic information regarding performances in these early cognitive areas in infants with DS, a description of the range of performances is informative. There was a wide range of performances on the four EF foundations tasks in both groups. Though the TD group was, on average, one second faster in their mean latencies to shift attention, it is also notable that there were infants in both groups who had mean latencies that were faster than one second. Despite having infants in both groups with similar attention shifting performances, the range in the group of infants with DS was three seconds greater. A similar wide range of performance was also observed in the early planning task. Although infants with DS had a larger range of latency to contact the ball (range of 27.26 s) than the TD group (range of 18.55 s), the majority of latencies for both groups clustered near one to two seconds. For the sustained attention measure, once again, a high degree of variability in performance was observed in the group of infants with DS (range of 94.1%) and the TD infants (range of 87.2%). Finally, the range of scores on the processing speed task was also similar for both groups, DS group = 129.06 and TD group = 121.87, with difference scores below 100 indicating habituation (the infant visually explored the object more on the first trial compared to the third) and difference scores above 100 indicating no habituation to the object (the infant visually explored the object more on the third trial compared to the first). See Table 2 for complete minimum and maximum value descriptions for the four EF foundation measures separated by group.

Table 2

*Descriptive Statistics on Foundational EF Measures*

	Mean (SD)	Minimum	Maximum
<b>DS (n= 58)</b>			
Attention Shifting Missing = 2	2.89 s (2.09)	.48	8.66
Sustained Attention	57.96% (20.61)	4.0%	98.1%
Early Planning Missing = 6	4.42 s (6.11)	.62	27.88
Processing Speed Missing = 9	91.10 (30.7)	22.33	151.39
<b>TD (n = 48)</b>			
Attention Shifting Missing = 12	1.80 s (1.17)	.24	5.68
Sustained Attention	41.11% (22.37)	0.7%	87.94%
Early Planning Missing = 6	3.41 s (4.60)	.57	19.12
Processing Speed Missing = 11	94.51 (26.46)	21.93	143.80

**Specific Aim 1: Group Differences in EF foundations**

**Group comparisons.** Group differences were observed on the dimension of sustained attention,  $t(104) = 4.03, p < .001, d = .78$ , at Time 1. Infants with DS looked for longer amounts of time during the sustained attention task (DS group  $M = 57.96\%$  time looking,  $SD = 20.61$ ; TD group  $M = 41.11\%$  time looking,  $SD = 22.37$ ). For the attention shifting and early planning task, performances were compared using a Mann-Whitney U test due to the non-normal distribution of the scores described previously. Differences were observed on the attention shifting task,  $U = 669.5, p = .007$ , and as mentioned above, infants with DS shifted their attention more slowly (DS group  $M = 2.89$  seconds,  $SD = 2.09$ ; TD group  $M = 1.80$  seconds,  $SD = 1.17$ ). The transformed version of the attention shifting variable (log transformation described in methods) showed the same result of group differences,  $t(90) = 2.90, p = .005, d = .63$ . Between-group differences were also observed on the early planning task,  $U = 782.0, p = .02$ .

For early goal-directed planning performances, infants with DS demonstrated longer average latencies to contact the balls,  $M = 4.42$  seconds,  $SD = 6.11$ , when compared to the TD infants,  $M = 3.41$  seconds,  $SD = 4.60$ . The transformed, categorical early planning variable (transformation described in methods) demonstrated the same pattern of group differences,  $t(75.5) = 2.09$ ,  $p = .04$ ,  $d = .50$ . In contrast to the other three measures, there were no significant between-group differences for the processing speed task,  $t(84) = .54$ ,  $p = .59$ ,  $d = .11$ . Based on scores from the processing speed measure, performance was categorized into two groups, infants who habituated (scores below 100) and infants who did not habituate (scores above 100). There were no significant group differences in the percentage of infants who habituated during the task,  $\chi^2(1, 86) = .524$ ,  $p = .47$ . Fifty-nine percent of the group of infants with DS habituated and 51% of the TD group habituated. See Table 2 for full descriptive statistics on foundational EF measures. The majority of missing data on the foundational EF measures (see Table 2) was due to a lack of administration of the task, but there was one case where the infant refused the task (processing speed task,  $n=1$ ) or there were examiner errors (early planning task,  $n = 2$ ). There were also two infants in the DS group and two infants in the TD group that had missing latencies on the early planning task because they did not make contact with the object.

Of the four proposed EF precursors, there was one measure, processing speed, that did not differ between groups. Because no group differences were identified, the processing speed task was subsequently excluded in further cross-sectional and longitudinal analyses. Uncertainty related to the accuracy of capturing habituation using this measure also contributed to the decision to exclude it. Excluding the processing speed variable avoided potential issues with construct validity in subsequent analyses and will be addressed in the limitations section of the discussion.



## Specific Aim 2: Foundational EF skills and Chronological Age

Different patterns of association were observed between CA and performance on the EF foundational cognitive tasks when comparing infants with DS and the TD equated group using bivariate Pearson correlations (see Table 3). In the group of infants with DS, there were moderate associations between CA and attention shifting, sustained attention, and early planning in the expected directions. Lower scores on the three foundational EF tasks, indicative of more regulated early cognitive performance, were associated with higher CA in the DS group. In the TD infants, there were relatively strong associations between CA and both attention shifting and early planning in the expected directions, such that lower scores on these two foundational EF tasks were associated with higher CA. Sustained attention was not significantly correlated with CA in the TD infant group,  $r(48) = -.06, p = .69$ . There were significant group differences between the early planning and CA correlation coefficients,  $Z = 1.71, p = .04$ , but no significant group differences in the correlation coefficients between attention shifting and CA,  $Z = .49, p = .31$ . See Table 3 for the complete correlation matrix.

Table 3  
*Bivariate Pearson Correlations for CA and EF Foundations*

<b>DS</b>	<i>1</i>	<i>2</i>	<i>3</i>
1. Chronological Age			
2. Attention Shifting	-.37**		
3. Sustained Attention	-.30*	-.11	
4. Early Planning	-.39**	.37**	-.09
<b>TD</b>	<i>1</i>	<i>2</i>	<i>3</i>
1. Chronological Age			
2. Attention Shifting	-.46**		
3. Sustained Attention	-.06	-.09	
4. Early Planning	-.66***	.46**	.16

Note. \* =  $p \leq .05$ , \*\* =  $p \leq .01$ , \*\*\* =  $p \leq .001$

To examine the relationships between CA, diagnostic status, and the EF foundational tasks, a multivariate multiple regression was completed. The independent variables included CA, diagnostic status, and CA x diagnostic status interaction, and the dependent variables were attention shifting, sustained attention, and early planning measures. The independent variables were found to be related to the set of dependent variables,  $F(9, 197.28) = 8.81, p < .001$ , and the three independent variables accounted for 56.1% of the variance in the set of EF foundation variables. Post-hoc examination of each dimension revealed that CA was related to the set of EF foundation variables, when controlling for diagnostic status, and CA x diagnostic status interaction,  $F(3, 81) = 17.79, p < .001, R^2 = .40$ . Diagnostic status was also significantly associated with the set of EF foundation variables, when controlling for the two other independent variables,  $F(3, 81) = 3.02, p = .03, R^2 = .10$ . Finally, the CA x diagnostic status interaction was related to the set of EF foundation variables, when controlling for the two other independent variables,  $F(3, 81) = 3.22, p = .03, R^2 = .11$ .

Univariate results confirm that CA was related to the attention shifting,  $F(1, 81) = 13.88, p < .001$ , and early planning,  $F(1, 81) = 43.21, p < .001$ , but not sustained attention,  $F(1, 81) = 2.74, p = .10$ . There was a significant association between diagnostic status and sustained attention,  $F(1, 81) = 6.04, p = .02$ , but no significant association detected between diagnostic status and attention shifting,  $F(1, 81) = .74, p = .39$ , or early planning,  $F(1, 81) = 1.14, p = .29$ . Finally, there was a significant association between the CA x diagnostic status interaction and early planning,  $F(1, 81) = 9.34, p = .003$  (see Figure 1), but no significant association between the CA X diagnostic status interaction term and attention shifting  $F(1, 81) = .59, p = .45$ , or sustained attention,  $F(1, 81) = 1.03, p = .31$ .

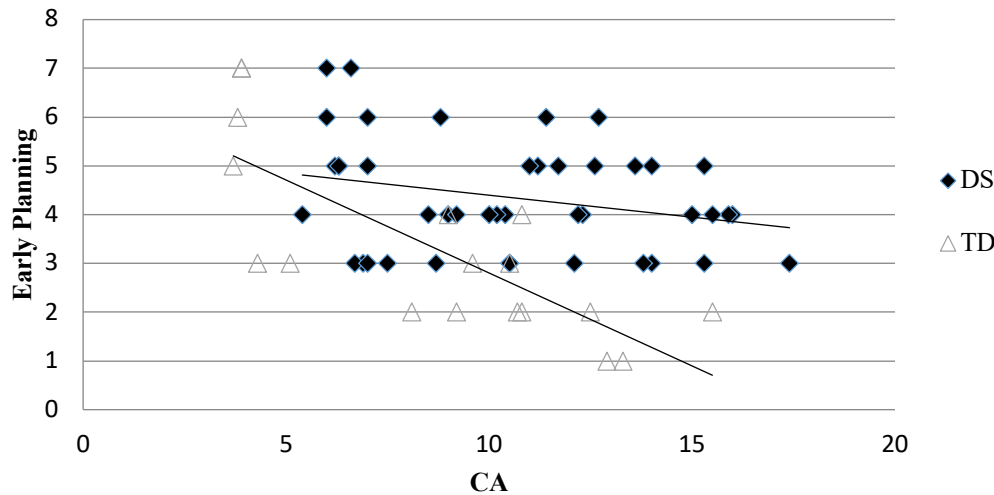


Figure 1  
*Interaction Effect of CA x Diagnostic Status and Early Planning Performance*

### Specific Aim 3: Relationship between EF Foundations and Early EF Skills in DS

A subset of the sample of infants with DS (n=40) completed a 6-month follow-up assessment, during which the A-not-B task was administered. Of the 40 infants who participated in the Time 2 visit, 50% were able to successfully complete the A-not-B switch and manually search for the toy in location-B. Within the set of infants who correctly located the toy post switch, half manually searched exclusively in location-B and the other half manually searched in location-B, followed by searching in location-A (“both locations, correct”).

To assess the relationship between cognitive EF foundations and early EF skills, a binary logistic regression was completed to examine whether group classification of success on the A-not-B task could be predicted by the three EF foundation variables (attention shifting, sustained attention, and early planning), controlling for cognitive ability at Time 2 and intervention condition when appropriate. Results of the binary logistic regression indicated that there was a significant association between the independent variables and post switch A-not-B performance,  $\chi^2(5) = 11.42, p = .04$ , Nagelkerke R Square = .331, -2 Log likelihood = 44.04. Attention

shifting was a significant predictor in the model such that for each unit increase in attention shifting (slower attention shifting), infants were 98% less likely to complete the A-not-B task successfully, Wald (1) = 5.46, SE = 1.62,  $p = .019$ , Exp (B) = .02, 95% CI : .001- .54. No other variables included in the model were significant predictors of A-not-B performance. Overall, the model correctly classified 75% of cases.

## CHAPTER 4 DISCUSSION

This study aimed to examine the developmental origins of EF challenges in infants with DS. EF foundational skills, including attention shifting, sustained attention, processing speed, and early planning, were evaluated in infants with DS and a TD comparison group to identify areas of early cognitive risk in DS at Time 1. In the group of infants with DS, longitudinal associations between these constructs and performance on an early EF task at Time 2 (6 months later) were also characterized. Attention shifting was found to be a significant predictor of early EF performance in the DS group, such that faster shifting of attention at Time 1 was associated with successful shifting on the A-not-B task at Time 2. In addition, there were observable differences in EF foundations during infancy at Time 1, suggesting that specific cognitive delays related to the underpinnings of EF skills are detectable in infants with DS. The association between CA and early planning was weaker in the DS group than the TD group, demonstrating the variation in the connection between early cognitive skill and CA between groups. Findings from this study add to the growing literature on early cognition in infants with DS and provide an important first step toward identifying early neuropsychological risk in this population.

### **EF Foundations and Early EF Skills in DS**

The most notable finding from this study was the significant relationship between EF foundational skills in infants with DS and subsequent early EF performance six months later. As hypothesized, average latency to shift attention was predictive of the shifting required for successful performance on the A-not-B task. There are several potential hypothesized explanations for this association. First, it is plausible that the construct of emerging EF begins as infant attention flexibility and develops into flexibility of searching behavior on the A-not-B

task. It may also be that both performances were contingent on the ability to take in perceptual information about multiple spatial locations. The early ability to attend to the two spatial locations in the infant shifting task may serve as a foundation for a later, more sophisticated ability to represent the two potential locations of the toy in the A-not-B task.

Another possible explanation for the association between attention shifting and later A-not-B performance relates to rudimentary inhibition skills. To shift attention quickly, infants must inhibit distractors in the environment. Correspondingly, successful performance on the A-not-B task requires the inhibition of motoric responses to the repeated location-A when the toy was switched to location-B. In this way, early resistance to distraction may lay a foundation for the more advanced motor inhibition necessary for success on the A-not-B task. Although there are multiple hypothesized explanations for this relationship, the continuity between attention shifting and later EF performance signals that attention shifting may be an indicator of risk for later EF challenges.

**Attention regulation replication.** This study on EF foundations in infants with DS replicated patterns of associations that have been reported in TD samples. Cognition and attention in TD infants have been linked to later EF performance during early childhood and adolescence in numerous studies (Cuevas & Bell, 2014; Rose, Feldman, & Jankowski, 2012; Rose, Feldman, & Jankowski, 2016; Rothbart, Sheese, Rueda, & Posner, 2011). The replication of this association in infants with DS provides evidence that the cognitive systems responsible for early EF skills function similarly in infants with TD and DS, despite the delayed cognitive skill acquisition observed in DS. This similar relationship is significant because longitudinal studies in TD populations can inform our understanding of the long-term implications of deficits in EF foundational skills detected in infants with DS. Future studies should investigate whether

similar patterns of association between infant cognitive foundations and EF skills continue over time in children and adolescents with DS.

Although this is the first study to report longitudinal connections between infant attention shifting and early EF in DS, it is not the first to identify attention regulation as an important developmental skill in this population. A previous study comprised of a subsample of participants in the present study reported a significant relationship between attention shifting and overall cognitive skill acquisition in infants with DS (Fidler et al., 2019). The current study extends these findings and reports longitudinal associations between early attention shifting skills and later cognitive flexibility, inhibition, and working memory skills. Taken together, findings from these two studies suggest that infant attention shifting may have significant implications for cognitive development in DS. Efforts should be made to replicate the results with a different sample of infants to verify the reported relationship.

**Other EF foundations.** It is also notable that two other foundational constructs measured at Time 1, sustained attention and early planning, were unrelated to EF performance at Time 2 in the DS sample. Though it may, indeed, be the case that these two skills are simply not predictive of early EF skills in infants and young children with DS, there are other possible explanations for these null results. The lack of association between sustained attention and later EF, for example, may result from the changing nature of looking times throughout infancy. Early in infancy, longer looking times represent the inability to disengage attention (sticky fixation), however, later in infancy, longer looking time represents sustained attention (Colombo & Mitchell, 2009; Kannass, Oakes, & Shaddy, 2006). The relatively broad age range of the infants in this study may include infants who demonstrated longer looking time because they were able to sustain attention as well as infants who demonstrated longer looking times because of sticky fixation

(Atkinson, Hood, Wattam-Bell, & Braddick, 1992). This confound complicates the interpretation of the association between looking time during infancy and later EF. Similarly, the lack of association between early planning and subsequent EF performance may be explained by the importance of motoric reaction times for the early planning task. It may be that infants with DS have slower motoric reaction times than TD infants, even though their cognitive planning skills may have been similar. This would result in longer latencies in early planning foundations for the infants with DS that may not be predictive of later EF performance.

In addition to the theoretical explanations for the lack of association between sustained attention and early planning and later EF performance, there are methodological considerations that warrant discussion. It is plausible that other mediators or moderators have a greater impact on the development of executive skills outside of the examined EF foundation domains, such as biomedical risk factors or intensity of early intervention services and therefore EF foundations do not fully explain the observed variations in EF performance. Additionally, each EF foundational skill domain was assessed using one task, which limits the certainty that the measures are accurately capturing the intended constructs. To address these issues, future studies should continue to characterize the contributions of mediators and moderators to the variability in emerging EF skills in DS and use multiple measures to increase confidence in the validity of the measurement tools.

### **Group Differences**

The longitudinal findings reported in the section above identify important associations between early attention regulation in infants with DS and later EF skills. Attention shifting, in particular, was identified as a significant predictor of emerging cognitive flexibility, inhibition, and working memory performance. However, to develop or utilize existing attention regulation



intervention techniques to support early EF, it is important to have a more detailed understanding of early performance on foundational cognitive tasks in infants with DS. To address this gap in our knowledge, the current study compared performance between infants with DS and TD infants on early cognitive foundations at Time 1.

A key finding from this comparison was the contrast in EF foundational skills across the two groups. The reported differences are especially notable, as the two groups were equated on overall cognitive level. Even after equating groups, the infants with DS, on average, demonstrated poorer than anticipated performances in attention shifting and early planning, as described below. Additionally, infants with DS sustained attention longer than TD infants, which may be attributed to the changing nature of attention in infancy and will be discussed.

**Attention shifting.** Infants with DS demonstrated slower attention shifting latencies when compared to TD infants, and these slower latencies have important developmental implications. Slower rates of attention shifting reflect early differences in the development of the attentional system in DS, which is the neuropsychological modality through which infants engage with the social and physical world. Although the mean group difference in attention shifting latency was approximately one second, this difference is clinically meaningful and likely to impact infants with DS in a variety of contexts. For example, if infants with DS have difficulty with orienting to objects and disengaging attention from objects, the pace of daily interactions is impacted, such that they may engage with fewer toys or objects throughout their day. Object play is important for early cognitive development in infancy, and the accumulation of fewer daily interactions, over time, may lead to diminished cognitive gains (Needham, 2000; Sommerville, Woodward, & Needham, 2005). Continuing to study the trajectory of attention shifting skills and

how this EF foundational skill impacts later cognitive and EF outcomes will be an important next step for research in DS.

**Sustained attention.** In addition to the attention shifting difficulties observed, infants with DS also demonstrated differences with sustained attention. On average, infants with DS looked at the novel object in the sustained attention task for longer periods than their TD counterparts. It was hypothesized that infants with DS would sustain attention for shorter durations, so the observed longer durations of looking were unexpected. As previously mentioned, there are several possible interpretations of this finding, as looking time represents different underlying processes at various stages of infancy. Toward the end of the first year, longer looking times are thought to indicate the ability to sustain attention and resist distractors to encode an object efficiently (Colombo & Mitchell, 2009; Kannass et al., 2006). Applying this interpretation, longer looking times in this study could signify that infants with DS resisted distractors and performed better on the sustained attention task than the TD infants. However, during the first 3 to 6 months of development, longer looking time is interpreted differently and is thought to indicate sticky fixation (inability to disengage attention) and slower processing speed (Atkinson et al., 1992; Colombo & Mitchell, 2009; Johnson, Posner, & Rothbart, 1991; Kulke, Atkinson, & Braddick, 2017). With this interpretation, infants with DS may have demonstrated *poorer* attention regulation and processing speed, due to the deficits in disengagement of attention and extended time needed to encode the object. Given the broader pattern of between-group comparisons, it is likely that longer looking times in DS are explained by sticky fixation, as it is unlikely that the infants with DS were showing more developmentally advanced performances than the TD infants on this particular dimension, but not others. If this interpretation is correct, this sticky fixation signals that infants with DS experience early

challenges in another aspect of attentional processing that may disrupt the development of cognitive foundations for more complex attention regulation skills.

**Early planning.** Along with group differences in various aspects of early attention regulation, this study also reported between-group differences on a third foundational skill for the development of EF, early planning. On average, latencies to contact the objects in the group of infants with DS were slower than those in the TD comparison group. There are multiple hypotheses about which aspects of development contribute to the observed differences in the early planning task. One relatively straightforward interpretation of these results is that motor delays in infants with DS (de Campos, Rocha, & Savelsbergh, 2010) generate slower latencies. However, due to the combined visual appraisal and motor output required for this early planning task, there is reason to consider an alternative interpretation of results that attributes slower latencies in DS to both cognitive and motor task components. It may be the case that, in addition to motor delays, infants with DS process perceptual information regarding the location of the object more slowly and take longer to mentally represent the goal of reaching for the object compared to TD infants. Early deficits in the production of basic planful acts (i.e., mentally representing and reaching for an object) are important to identify, as deficits with these basic skills could contribute to more pronounced gaps in later planning and EF challenges in DS beyond infancy.

**Processing speed.** Although neuropsychological differences were identified in three EF foundations (attention shifting, sustained attention, and early planning), there were no group differences observed on the visual habituation task that measured processing speed. This discrepant finding was surprising considering the slower processing speed observed in DS (Brooks-Gunn & Lewis, 1984). There are several possible explanations for the reported

equivalent performances. First, it may be the case that the groups do not, indeed, differ in performance on this dimension and were truly showing similarities in performances in processing speed. While this is one possible interpretation, there are also potential confounds to consider that may have compromised the construct validity of the visual habituation measure. First, it is possible that infants habituated to the spoon in a shorter period than the 90-seconds of the processing speed task. This may have contributed to the lack of group differences because the measure did not capture the exact moment when habituation occurred, which likely varied between groups. Another plausible interpretation of the results is related to infants' early experiences with spoons (the object used in the task). More accumulated experiences with spoons in the TD infants may have increased overall interest in the object, as it may have evoked anticipation for food. If the object was not food-related, the TD infants may have lost interest (i.e., demonstrated habituation) at a faster rate compared to the infants with DS. Therefore, while there were no group differences observed, it is likely that the specific task-related limitations explain the lack of variation between groups, which raises questions regarding the utility of the visual habituation task as a measure of processing speed in the current study.

### **Heterogeneity in Performances**

Although the between-group differences reported in this study were pronounced, there was also a substantial amount of task performance variability in the DS group. There was non-syndrome-related variability observed in the TD group, which may be related to comorbid conditions observed in the general population, however, it was relatively modest compared to the DS group. This substantial heterogeneity in performance in the DS group includes instances where individual infants with DS performed comparably to TD infants on EF foundational tasks, along with cases where performances were markedly lower than the TD and DS group averages.

Understanding individual difference is clinically relevant for the detection of risk in this population because there may be specific indicators of early cognitive risk related to later, more profound cognitive impairments in DS.

Notably, there were individual performances in infants with DS that paralleled their TD counterparts. For example, on the attention shifting task, several infants with DS demonstrated average latencies that were less than one second, which was comparable to performances observed in the TD group. On the early planning task, both groups included cases of latencies to touch the object that were less than one second. Performance on the sustained attention task was similar in both groups, such that there were individuals who looked at the object for short periods (i.e., less than 5% of the time) and long periods (i.e., more than 85% of the time). These DS and TD group similarities demonstrate that, despite overall group differences, a subset of infants with DS demonstrate early skill acquisition that is similar in nature to TD infants. Recognizing areas of strength in individual cases can guide the selection of skills to be leveraged in personalized treatments for infants with DS.

The heterogeneity of performance observed in the DS group also revealed cases in which individuals with DS performed markedly poorer than TD infants and DS group averages. This was especially true regarding the attention shifting and early planning variables. For example, the maximum latency to shift attention in the infants with DS was three seconds greater than the maximum latency observed in the TD group. Three outliers in the group of infants with DS were also removed because of their markedly longer latencies to shift attention. As such, the average latency to shift attention reported in the results does not fully represent the range of deficits in this cognitive foundation. Similar cases of slow responses were observed in the early planning task. The most impaired individual performances in the groups of infants with DS were

approximately 10 seconds slower than in the TD group. This greater heterogeneity in performance within DS is in line with findings observed in children and adults who show considerable individual differences in cognitive abilities (Karmiloff-Smith et al., 2016). Infants who demonstrate EF foundational challenges compared to other infants of a similar overall cognitive level may have increased risk for comorbid conditions, and more studies are needed to examine whether this subgroup of infants would benefit from increased intensity of intervention services.

### **EF Foundation Performance and Chronological Age**

In addition to characterizing similarities and differences in foundational EF performance between groups, this study also investigated the cross-sectional relationship between foundational EF skills and CA. CA is closely yoked to skill acquisition in TD infants and it is understood that as time passes, there are interdependent cognitive, motoric, and social skills that develop in the general infant population. While these skills track closely to CA in TD infants, the relationship may be disrupted within DS due to global developmental delays and heterogeneity observed in this population. Therefore, understanding the association between CA and EF foundational skills is an important first step to identifying specific areas of cognitive and overall developmental risk within the first two years of development in DS.

In this study, a distinctive pattern of association was observed at Time 1 between CA and EF foundation variables, such that higher CA was associated with better performance on the EF foundation measures (lower EF foundation scores indicated better performance). In both groups, attention shifting and early planning were negatively correlated with CA, and higher CA was associated with shorter latencies to shift attention and make contact with objects. This same pattern was present for sustained attention in the group of infants with DS and higher CA was

associated with less sticky fixation. One interpretation of these results is that the time accounted for with CA affords infants in both groups opportunities for interactions that stimulate skill acquisition, and are connected to performance on EF foundational tasks. It is possible that daily interactions with objects and social partners support the development of each of these foundational cognitive skills. For example, with repetition, infants incrementally gain more knowledge about objects by attending to them and learn to make directed arm movements towards a caregiver more rapidly to initiate a social interaction. Notably, even though the association between CA and EF foundations is weaker in the infants with DS, it is still present, signaling that CA may be an important variable for interpreting ongoing skill acquisition in this population. A precise understanding of the relationship between CA and early cognitive skills will aid clinicians in identifying early risk in their patients, as they will be able to track expected changes in early cognition relative to CA in DS.

Although both groups showed a similar direction of the association between EF foundations and CA, the relationship was stronger for the association between early planning and CA in the group of TD infants. The pattern of different strengths of association was further informed by subsequent regression analyses. The interaction between CA and diagnostic status significantly predicted early planning performance, which indicated there was a different pattern of association between groups (see Figure 1), such that there was a stronger relationship between CA and early planning in the TD group of infants. The difference in magnitude of association between groups is relevant for understanding how early planning unfolds differently in connection to CA in DS. It is possible that in the group of infants with DS, other mediating factors cause variability in early planning skills, and therefore the strength of the relationship

was not as pronounced as it was in the group of TD infants. Therefore, CA is likely to only be of modest predictive value of foundational EF skills in DS compared to TD infants.

Despite the differing patterns of association between early planning and CA, there were no interaction effects observed in the associations between CA and attention shifting or sustained attention. Although there was a slightly stronger association between CA and attention shifting in the TD infants than the infants with DS, this difference was not significant. It is plausible that the relationship between CA and attention shifting does not differ between groups. It could alternatively be the case that this difference was not detected due to the modest sample size in the study. Furthermore, there was also no association between CA and sustained attention observed in the TD group and thus, there were no differences identified in varying magnitudes of association between groups. One possible interpretation for the lack of association in the TD group is the range of CAs included in the study. It may be the case that large visual percentages on the sustained attention task were young infants who experienced sticky fixation and older infants who exhibited advanced attentional control. Therefore, no clear connection could be made with CA given the differing possibilities for observations on the sustained attention task. Identifying and interpreting the patterns of association that do not differ by group or correspond with CA is critical for understanding the association between CA and EF foundational skills in both infants with TD and DS.

### **Intervention Implications for Supporting Early EF**

Investigating precursors to EF performance is critical because infants with DS may benefit from earlier participation in targeted interventions to supplement the services provided when EF challenges are present during the toddler and preschool years (Daunhauer et al., 2017). Optimizing early interventions that support EF skill development is especially important in DS



because EF challenges persist into adulthood (Tomaszewski et al., 2018; Wilde & Oliver, 2017). Therefore, there is a pressing demand for personalized treatments in this population, and infants and young children will likely benefit from interventions designed to target the earliest presentation of EF difficulties. Though there are a limited number of available interventions, understanding the areas of challenge in DS (i.e., attention shifting) that are associated with early EF will make it possible to implement existing techniques and develop new phenotype-informed interventions that will support the development of EF skills from an early age.

The strong link between early attention shifting and later EF performance suggests that attention skills during infancy should be considered as a potential target for intervention in infants with DS. This intervention target is particularly promising because previous studies have demonstrated the plasticity of attention regulation skills during infancy (Bryck & Fisher, 2012; Kovacs & Mehler, 2009; Swingler, Perry, & Calkins, 2015). One recent study showed that computer-based training improves attention regulation in 11-month old TD infants (Wass, Porayska-Pomsta, & Johnson, 2011). The training consisted of four attention tasks that targeted visual searching and shifting, inhibition of distractors, and working memory, and task difficulty varied based on infant performance. Infants in the training condition demonstrated reduced visual reaction times and shortened response periods to disengage their attention (Wass et al., 2011), which directly relates to components of the attention shifting task from the current study. Interventions of this nature are potentially feasible for infants with DS and should be explored in future studies to determine whether modifications or phenotype-sensitive adaptations might be necessary for this population.

Another intervention that has potential value for supporting EF foundational skills is designed to target the development of reaching behavior in infancy (Needham et al. 2002). This

reaching intervention has been tested in DS and a portion of the infants in the current study participated in the treatment condition for the intervention (Fidler et al., under review). Although the reaching intervention has not been directly linked to EF outcomes, studies completed with TD infants have shown cognitive gains up to 12 months after performing the facilitated reaching activities (Libertus et al. 2016; Needham et al. 2002). The current study did not find significant differences in early EF performance based on intervention participation, however, only part of the group from this study participated and not all infants received the intervention in the most impactful developmental window (Fidler et al., under review). Investigating how facilitated reaching activities may benefit EF and cognitive development over time will be an important next step for intervention science in DS.

Despite the small number of empirically tested infant interventions targeting EF precursors, previous studies offer insight into future directions for intervention strategies. One potential idea to be explored in future intervention studies is a caregiver-focused approach. Multiple studies have found that caregivers influence the development of attention regulation during infancy (Calkins & Hill, 2007; Spinrad & Stifter, 2002; Waxman & Spencer, 1997) and investigating the most effective ways for parents to support early regulatory processes is one possible direction for future applied work. Another approach may be to modify existing EF training programs for preschoolers (Diamond & Lee, 2011) to be developmentally appropriate for infants within the first two years of life. Taken together, targeting EF precursors with a variety of intervention approaches will be important for intervening effectively with populations vulnerable to EF deficits.

The current study also observed group differences in the percentage of Hispanic participants across groups that are important to consider for intervention development within DS.

There was a larger percentage of Hispanic individuals in the group of infants with DS than the TD group. It may be the case that this underserved population self-selected into the broader intervention study from which these data originated. Another plausible interpretation of this ethnic difference was related to variability in prenatal screening and family planning practices across groups. Therefore, cultural values from a variety of groups should be accommodated in prospective intervention strategies. Future interventions should consider the best ways to support underserved families and provided culturally sensitive intervention techniques within the DS community.

### **Limitations**

The present study has several limitations that should be considered when interpreting the results. One limitation of the study is that each infant EF foundational construct was assessed using only one laboratory measure. The use of only one measure per construct makes the study more vulnerable to measurements that do not have adequate construct validity. Additionally, for the TD sample, data were collected exclusively at one time point, which restricts the comparisons that can be made between groups longitudinally. There was also only one follow-up visit completed for the group of infants with DS. Future studies should include TD comparison groups for all time points, along with additional longitudinal visits to examine changes on more sophisticated EF related outcomes over longer periods.

Another consideration is that the sample size was modest, which restricted the generalizability of the findings and increases the risk for type II error. Future studies should attempt to replicate the study with a larger sample size. Additionally, the sample of infants with DS had a greater degree of variability in task performance than the TD group. This is commonly

observed in individuals with DS (Karmiloff-Smith et al., 2016), however, there is no guarantee that the full range of performance in the group of infants with DS was represented in the sample.

Several methodological limitations are worth noting as well. For example, the processing speed variable was collected on a fixed time scale (three set trials of 30-seconds) rather than in contingency with infant behavior. With a fixed time scale, infant independent exploration was measured, rather than examining the decreasing rate of interest throughout repeated presentations across a greater number of trials. This means that rather than calculating a rate of habituation, the differences in visual interest over the 90-second period were captured by comparing the total exploration time between the first and third trials. This may have been problematic because infants may have habituated within the first 30-second trial, which would make the observations on the third trial inconsequential, and subsequent difference scores difficult to interpret. Using difference scores also limits the interpretability of the results because markedly different performances on the task could have resulted in the same score. For example, one individual infant could have visually explored the object for 15% of the first trial period and 5% of the third trial period. Another infant could have visually explored the object for 100% of the first trial period and 90% of the third trial period. These performances vary in the total amount of visual exploration, however, the difference scores are the same, which restricts the interpretation of scores for this task. Because of these methodological and interpretation issues, the processing speed measure was removed from further analyses to avoid probable issues with construct validity in the current study.

A final limitation of this study is that the group of infants with DS and TD had significantly different CA ranges and the mean CA in the group of infants with DS was 3.5 months older than the TD comparison group mean. The current study was focused on answering

research questions with groups equated on cognitive developmental age, however, future work could also include a group of CA-equated infants to answer additional questions regarding the CA differences in early cognitive development in DS. This comparison will allow for the description of the precise timing that early EF foundations deviate from the typical developmental trajectory and determine what other developmental factors are associated with those deviations.

### **Future Directions**

This study provides important novel information regarding the atypical presentation of EF foundational skills that are predictive of subsequent EF performance in infants with DS. Future research should explore the association between infant performance and longer-term cognitive outcomes to identify areas of early cognitive risk that are connected to comorbid conditions. It may also be the case that early cognitive variables in infancy relate to more sophisticated cognitive skills that develop later in childhood. Previous studies on TD children follow participants from infancy to age 3 or 4, and some studies even into adolescence (Cuevas & Bell, 2014; Rose et al., 2012; Rose et al., 2016; Rothbart et al., 2011). Therefore, longer-term follow-up assessments are warranted to improve our understanding of how cognitive foundations cascade onto EF skills in early childhood or identify risk for potential comorbidities.

Additional studies should also expand on the variables used to measure infant cognition. Though the current study examined multiple indicators of infant foundational skills, there are many ways to capture infant neuropsychological functions that were not utilized in the current study. Including a more precise indicator of eye saccade reaction time or a measure of caregiver reported infant self-regulation would improve the exactness and breadth of the conclusions. By

increasing the number of measurements at the first time point, there would be a greater chance of capturing variability in infancy that relates to differences in emerging EF skills.

Finally, many intraindividual and environmental variables are likely related to the early development of EF in young children with DS outside of early cognitive skills. One variable that should be considered in future work is maternal sensitivity and responsiveness, which has been found to be related to the development of EF in young TD children (Bernier, Carlson, & Whipple, 2010; Mahoney & Nam, 2011). Another variable likely to contribute to EF development is gross motor skills, and specifically, trunk control. Early trunk control has been connected to attentional skills and it is hypothesized that recruiting resources to maintain this gross motor movement may take away from resources available to be devoted to cognitive actions in infancy (Berger, Harbourne, & Gualpa Lliguichuzhca, 2019; Berger, Harbourne, & Horger, 2018). This is of particular interest to the study of infants with DS, a population at risk for gross motor delays (Winders, Wolter-Warmerdam, & Hickey, 2019). The age of participants in the current study also did not allow for the examination of handedness and the relationship to EF and should be considered as a future outcome of interest. Finally, a broader look at access to intervention is another area that warrants further examination related to early EF development. While these variables were not included in this study, it is likely that they account for a portion of the variability in early EF performance and should be pursued in future studies.

### **Broader Implications**

Although the current study focused on a specific set of early cognitive tasks and early EF measurements, the findings have implications for understanding early cognition in infants with DS more broadly. Attention shifting was identified as one EF precursor skill, which supports the hypothesis that it is possible to detect early developmental risk in this population. If early

developmental risk for EF deficits can be recognized, there is a strong likelihood that early risk for other co-occurring conditions, such as attention deficit hyperactivity disorder and autism spectrum disorder, can also be detected. The process of identifying specific areas of cognitive risk for infants with DS is an important next step for the field and will inform the development of phenotype-sensitive early interventions. There is a substantial amount of heterogeneity in young children with DS and having the tools to recognize areas of risk and intervene when appropriate will improve personalized precision medicine for this population.

## **Conclusions**

This study investigated the precursors and developmental origins of EF deficits in infants with DS. Group differences in cognitive foundations, including attention shifting, sustained attention, and early planning were identified between infants with DS and their TD counterparts. In the group of infants with DS, the predictive nature of each cognitive foundation was evaluated at a 6-month follow-up and attention shifting emerged as the single predictor of early EF performance on a cognitive flexibility, inhibition, and working memory task. Identifying areas of cognition in infants that are connected to early EF equips service providers with knowledge to support personalized care in this area of known challenge for young children with DS. Early intervention that supports attention shifting and regulation will optimize the growth trajectory of EF skills and, ultimately, has the potential to improve cognitive outcomes in this population.

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